Synthesis of New 1,1′-Carbonyl-bis[3-aryl(heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] and Trifluoromethyl Derivatives through Ring-Opening Reactions

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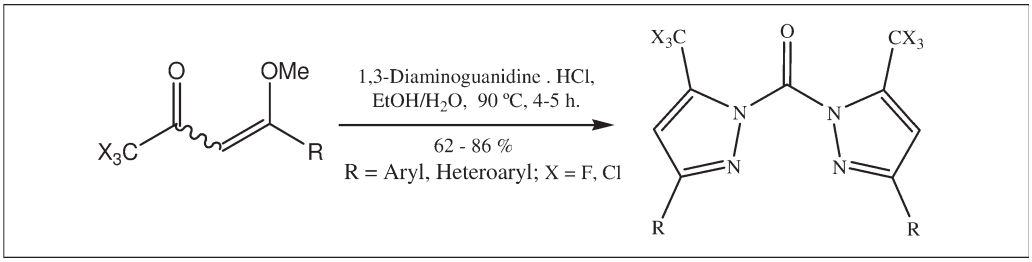

Two new series of 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-trihalomethyl-1*H*-pyrazoles], where aryl = C_6H_5, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-$OCH_3C_6H_4$, 4-$NO_2C_6H_4$, 4,4′-BiPh, 1-naphthyl, and heteroaryl = 2-thienyl and 2-furyl have been synthesized, in a one-pot methodology, from the reaction of 4-methoxy-4-aryl(heteroaryl)-1,1,1-trihalobut-3-en-2-ones with 1,3-diaminoguanidine monohydrochloride. The heterocycles were obtained regioselectively in good yields (62–86%) and in a short reaction time. Ring-opening reactions with 1,2-dinuleophiles and the synthesis of ethyl carboxylate derivative from a pyrazolycarbohydrazide is also reported.

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INTRODUCTION

The linked pyrazole ring represents an interesting block for synthesis strategies as well as studies on their biological and chemical properties. Moreover, pyrazoles are a class of heterocyclic compounds with many derivatives, and of note, the fluorinated pyrazoles have been demonstrated to play key pharmacophore functions in many pharmaceutical and agrochemical fields [1,2].

The introduction of fluorine(s) into heterocyclic rings is still limited and the trifluoromethyl substituted α,β-unsaturated ketones represent a practical way to access such compounds [3–11]. In recent years, the synthesis of trifluoromethyl pyrazoles has drawn much attention and the literature has reported a series of specific 5-CF_3 substituted pyrazoles. The main synthetic methods to prepare such compounds involve CCC and NN atom fragments in cyclization reactions of substituted hydrazines or derivatives thereof with 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones [3–9].

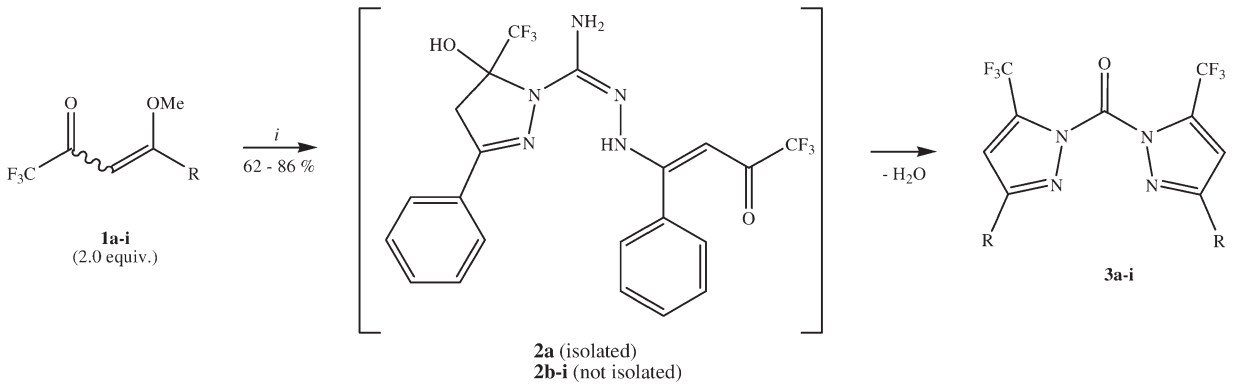
This [3+2] cyclization approach has been shown to be an efficient method to prepare such compounds, where the pyrazole ring is linked to another pyrazole. On the other hand, carbonyl-bispyrazoles are not so common in the literature. For instance, new synthetic routes to obtain these compounds and studies on their potential as pharmaceuticals and agrochemicals have been relatively little explored [10–12].

1,1′-Carbonyl-bispyrazoles have been most commonly synthesized by substitution reaction involving phosgene and other derivatives with pyrazoles [13–19]. However, this synthetic procedure is efficient only when the starting materials are symmetric substituted or nonsubstituted pyrazoles, because nonsymmetric 3- or 5-substituted pyrazoles may exist in two tautomeric structures in solution and their N^1-substitution reactions lead undoubtedly to three possible carbonyl-bispyrazoles isomers.

Soliman and Darwish [13] have reported that substituted 3,5-dimethyl-1*H*-pyrazoles reacted with ethyl chloroformate, in the presence of anhydrous potassium carbonate, giving bis-(3,5-dimethyl-1*H*-pyrazole)methanone, in good yields, as a possible hypoglycemic agent. However, a very limited scope is observed when the bis-pyrazole synthesized by this procedure has only methyl substituents at the position 3 and 5 of both pyrazole rings.

More recently, Higgs and Carrano [20] reported the synthesis of carbonyl-bispyrazoles prepared by the

Scheme 1. Synthetic route to prepare bis-pyrazoles **3**. Reagents and conditions: (*i*) 1,3-diaminoguanidine. HCl (1.0 equiv), EtOH/H_2O, 90°C, 4–5 h.



1-3	a	b	c	d	e	f	g	h	i
R	C_6H_5	4-$CH_3C_6H_4$	4-FC_6H_4	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$	4,4'-BiC_6H_4	2-Naphthyl	2-Thienyl	2-Furyl

reaction of 3,5-substituted 1*H*-pyrazoles (R and R^1 = H, CH_3, *i*-Pr) with phosgene, using triethylamine in anhydrous THF as solvent. In this procedure, symmetric carbonyl-bispyrazoles (R = R^1 = H or CH_3) were obtained, except when R = H and R^1 = *i*-Pr. In the previous example, a mixture of isomeric bis-pyrazoles was not obtained due to a steric hindrance between the *i*-propyl substituents.

Recently, we have reported the one-step and regioselective procedure for the synthesis of a novel series of 1,1′-carbonyl-bis[3-alkyl(aryl/heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles] [21] from the cyclocondensation reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones with carbohydrazide. Subsequently, as an example, 1,1′-carbonyl-bis(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazole) was subjected to dehydration reactions, using acetic acid/ethanol [22,23], at reflux for 4 h or sulfuric acid/ethanol [24] at reflux for 4 h. In both the cases, the aromatic 1*H*-pyrazole was obtained with the simultaneous removal of the carbonyl function. Because of the relative elimination difficulty, the presence of trifluoromethyl, and the carbonyl groups at positions 5 and 1 of the pyrazole, respectively, another synthetic procedure was performed. After a review of the literature and in an attempt to obtain the aromatic bis-pyrazole, we chose thionyl chloride/pyridine [24,25] as the dehydration agent. Again, the isolation of 1*H*-pyrazole was observed with the cleavage of both C(O)—N bonds.

RESULTS AND DISCUSSION

As an alternative strategy for the synthesis of trifluoromethylated aromatic bis-pyrazoles, in this study we describe firstly the full regioselective synthesis and characterization of a new series of 1,1′-carbonyl-bis(3-substituted-5-trifluoromethyl-1*H*-pyrazoles) (**3**) from the reaction of trifluoromethyl vinyl ketones (**1**) with 1,3-diaminoguanidine monohydrochloride (Scheme 1).

In principle, β-alkoxyvinyl trihalomethyl ketones (**1a–i** and **8a–f**) are prepared by trihaloacetylation reaction of acetals derived from ketones, according to the previously described procedures [5,26–28].

1,1′-carbonyl-bis(3-substituted-5-trifluoromethyl-1*H*-pyrazoles) (**3a–i**) were obtained from the reaction of two equivalents of 4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1a–i**) and one equivalent of 1,3-diaminoguanidine monohydrochloride, in a one-pot reaction and in 62 to 86% yields. All reactions were carried out in ethanol/water (20:1), monitored by TLC, and the optimal reaction time and temperature were 4–5 h at 90°C. After this time, the compounds (**3a–i)** were isolated by extraction with chloroform/water (1.5:1). The organic layer was dried and evaporated under reduced pressure. The products (**3a–i**) were purified by recrystallization from *iso*-propyl ether, to give pure yellow solids.

According to our previous experience, trifluoromethyl vinyl ketones **1a–i** readily react with substituted hydrazines to give only 5-CF_3 substituted pyrazoles [3–9]. In this study, we found that 1,3-diaminoguanidine monohydrochloride reacted specifically as a bis-1,2-dinucleophile with enones **1a–i** and **8a–f** to give bis-pyrazoles linked through a carbonyl carbon. As for the reaction mechanism, firstly, the cyclization of enones **1a–i** takes place furnishing 1,1′-carbonyl-bis(4,5-dihydro-pyrazole) intermediates linked through an imino group. These intermediates undergo *in situ* water elimination and hydrolysis of the imino group to give the respective bis-pyrazoles **3a–i**. The evidence of this mechanism is given

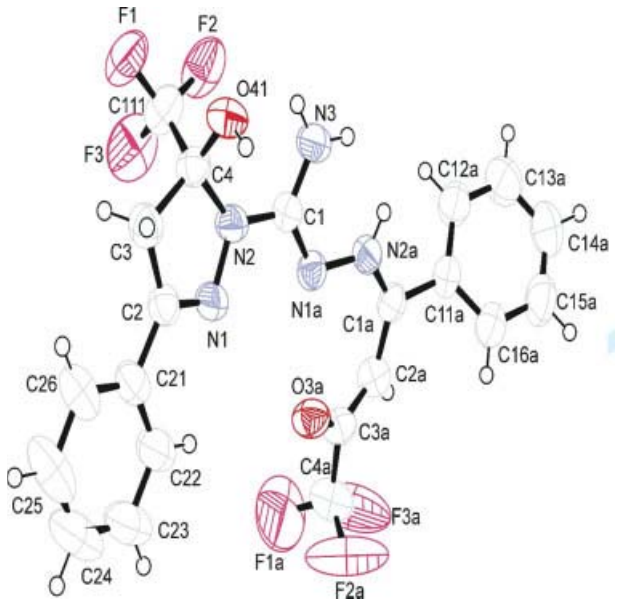


Figure 1. ORTEP plot of the intermediate **2a**. Thermal ellipsoids are shown at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

by the isolation of the intermediate **2a**, the only intermediate that was isolated and whose was structure confirmed by single-crystal x-ray diffraction (Fig. 1) [29].

The optimal condition to isolate product **3a** together with a trace of the intermediate **2a** was when the reaction was carried out in ethanol/water, at 90°C for 3 h.

The structures of **3a–i** and **9a–f** were deduced from their NMR spectra (^{1}H and ^{13}C) and by comparison with NMR data of other pyrazoles formerly synthesized in our laboratory [5–9].

The symmetrical carbonyl heterocycles **3a–i** show a symmetrical pattern with one set of signals for the hydrogens and carbons of the 3-substituted pyrazole rings. The compounds **3a–i** show the ^{1}H NMR chemical shifts in DMSO-d_6 for the H-4 as a sharp singlet in the range of 5.85–6.41 ppm. The signals for the other aromatic hydrogens are in the range of 6.53–8.23 ppm.

The compounds **3a–i** present the typical ^{13}C chemical shifts of pyrazole rings at an average of 148.1 ppm (C-3) and 86.7 ppm (C-4). The C-5 exhibit signals at around 169.3 and appear as a characteristic quartet with ^2J = 28 Hz, because they are attached to a CF_3 group. The CF_3 group shows a typical quartet at an average of 118.2 ppm, with $J_{C\text{-}F}$ = 291 Hz. The ^{13}C chemical shifts of the other aromatic carbons present a signal in the range of 113.2–147.3 ppm. The carbonyl carbon interfacing the two pyrazole rings shows signals in the range of 185.6 ppm.

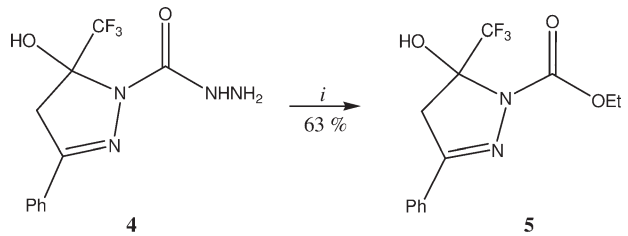
Subsequently, aiming to obtain examples of heterocyclic derivatives, the reaction of carbohydrazide **4** with a 1,3-diketone (2,4-pentanedione) was performed. In this case, the well-known ester **5** [30] was isolated in 63% yield, instead the desired nonsymmetrical bis-pyrazole, showing an interesting and promising employment of pyrazolyl carbohydrazides such as **4** (Scheme 2). Compound **4** was obtained when the reaction of pure carbohydrazide [$(NH_2NH)_2CO$] and 4-methoxy-4-phenyl-1,1,1-trifluorobut-3-en-2-one was carried out at a molar ratio 1:1, in ethanol, according to the literature [21].

Finally, the new ketone **3b** was subjected to reactions with phenylhydrazine [31] and hydroxylamine hydrochloride [32] to verify the possibility of an induced ring-opening reaction followed by recyclization with these two dinucleophiles (Scheme 3).

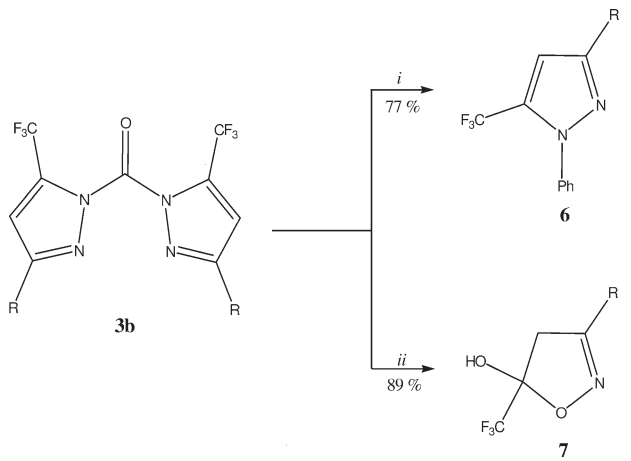
Although **3b** is not the best precursor to synthesize pyrazole **6** and isoxazoline **7**, these well-known heterocycles were easily isolated in good yields (77–89%) from this type of reaction.

In addition to the interest inherent in the chemical attributes of these novel trifluoromethylated condensation products **3**, it seemed appropriate to evaluate the cyclization reactions involving now the β-alkoxyvinyl trichloromethyl ketones **8a–f** and 1,3-diaminoguanidine monohydrochloride (Scheme 4).

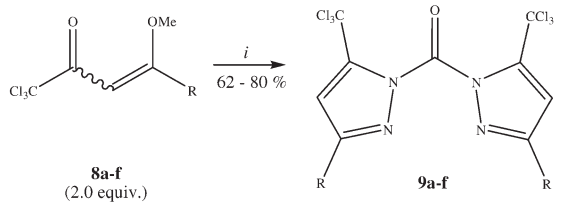
Scheme 2. Synthesis of nonsymmetrical ketone **5**. Reagents and conditions: (*i*) 2,4-pentanedione, EtOH, reflux, 20 h.



Scheme 3. Preparation of pyrazole **6** and isoxazole **7** from ketone **3b**. Reagents and conditions: (*i*) NH_2NHPh, EtOH, reflux, 4 h; (*ii*) $NH_2OH{\cdot}HCl$, Py, H_2O, 45°C, 24 h (R = 4-Tolyl).



Scheme 4. Synthetic route to prepare bis-pyrazoles **9**. Reagents and conditions: (*i*) 1,3-diaminoguanidine. HCl (1.0 equiv), EtOH/H_2O, 90°C, 4–5 h.



8a-f (2.0 equiv.) **9a-f**

8-9	a	b	c	d	e	f
R	C_6H_5	4-$CH_3C_6H_4$	4-ClC_6H_4	4-BrC_6H_4	4-$NO_2C_6H_4$	2-Thienyl

We reported now the results of reactions of ketones **8** with 1,3-diaminoguanidine monohydrochloride which were expected to deliver 1,1′-carbonyl-bis(5-trichloromethyl-1*H*-pyrazoles) **9a–f** bearing an carbonyl moiety on the newly formed bis-trichoromethyl substituted heterocyclic system. We carried out the reactions of 4-methoxy-1,1,1-trichlorobut-3-en-2-ones **8** with 1,3-diaminoguanidine monohydrochloride, in 2:1 molar ratio, respectively, and in ethanol/water (20:1) as solvent.

When the mixtures were heated at 90°C, after stirring for 4–5 h, the TLC showed that the reactions proceeded smoothly and gave the products **9** in 62–80% yields (Scheme 4). The derivatives **9** were all stable, white crystalline solids, which showed no significant signs of decomposition after being stored for many months under refrigeration and were unaffected by the recrystallization method.

NMR spectroscopic studies alone allow convincing structural assignments for this heterocyclic system and consequently unequivocal determination of structures of **9**. The symmetrical carbonyl heterocycles **9a–f** show a symmetrical pattern with one set of signals for the hydrogens and carbons of the 3-substituted pyrazole rings. The compounds **9a–f** show the ^{1}H NMR chemical shifts in DMSO-d_6 for the H-4 as a sharp singlet in the range of 6.21–6.98 ppm. The signals for the other aromatic hydrogens are in the range of 7.21–8.30 ppm.

The compounds **9a–f** present the typical ^{13}C chemical shifts of pyrazole rings in average of 175.0 ppm (C-3) and 85.6 ppm (C-4). The carbonyl carbon bonding the two pyrazole rings shows signals in the range of 182.8 ppm. The two CCl_3 groups show a typical singlet in average of δ 98.9 ppm. All the signals are consistent with ^{1}H and ^{13}C NMR chemical shifts of the pyrazoline moieties for these symmetrical systems.

In conclusion, we have developed a useful, simple, and convenient procedure to obtain new 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-trihalomethyl-1*H*-pyrazoles] (**3**, **9**), starting from the cyclocondensation reactions with β-alkoxyvinyl trihalomethyl ketones (**1**, **8**) and 1,3-diaminoguanidine monohydrochloride in a one-pot method leading to high yields (62–86%). In addition, the reaction was proven to be regioselective because only the 1,1′-carbonyl-bis(5-trihalomethyl-1*H*-pyrazole) isomer was isolated. Moreover, we think that alkylcarboxylate heterocycles such as **5** and many other ring-opening reactions can be induced in this new heterocyclic system using several dinucleophiles.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in DMSO-d_6 for **3**, **5**, **9** and in $CDCl_3$ for **6** and **7**, using TMS as internal reference. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and He was used as the carrier gas.

Synthetic procedures. General procedure for the preparation of 1,1′-carbonyl-bis[3-aryl(heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] (3a–i, 9a–f). A stirred mixture of 4-methoxy-1,1,1-trifluorobut-3-en-2-ones (**1a–i**) or 4-methoxy-1,1,1-trichlorobut-3-en-2-ones (**8a–f**) (2.0 mmol) and 1,3-diaminoguanidine monohydrochloride (1.0 mmol), diluted in ethanol (20 mL) and water (1 mL) was heated in an oil bath for 4–5 h at 90°C. After cooling, water (10 mL) was added to the reaction and the product extracted with chloroform (2 × 15 mL). The organic layer was dried (Na_2CO_3) and evaporated under reduced pressure. The solid residues were recrystallized from iso-propyl ether to give white solids.

1,1′-Carbonyl-bis(3-phenyl-5-trifluoromethyl-1*H*-pyrazole) (3a). This compound was obtained as a yellow solid, yield 75%, Mp. 211–212°C. ^{1}H NMR (DMSO-d_6) δ = 7.75–7.79 (m, 4H, aromatic-H), 7.38–7.42 (m, 6H, aromatic-H), 5.94 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 186.1 (C=O), 169.3 (C-5, J = 28), 141.7 (C-3), 130.2; 128.1; 126.8; 126.6 (aromatic-C); 118.2 (q, CF_3, J = 291), 87.3 (C-4).

1,1′-Carbonyl-bis[3-(4-tolyl)-5-trifluoromethyl-1*H*-pyrazole] (3b). This compound was obtained as a yellow solid, yield 80%, Mp. 241–243°C. ^{1}H NMR (DMSO-d_6) δ = 7.69 (d, 4H, Ar); 7.21 (d, 4H, Ar); 5.91 (s, 2H, H-4); 2.32 (s, 3H, Me). ^{13}C NMR (DMSO-d_6) δ = 185.6 (C=O); 169.3 (q, ^2J = 28, C-5), 152.9 (C-3), 128.7, 128.5, 126.7, 126.5 (6C, Ar), 122.1 (q, ^1J = 291, CF_3), 86.8 (C-4), 20.7 (Me).

1,1′-Carbonyl-bis[3-(4-fluorophenyl)-5-trifluoromethyl-1H-pyrazole] (3c). This compound was obtained as a yellow solid, yield 79%, Mp. 179–181°C. ^{1}H NMR (DMSO-d_6) δ = 7.85 (t, 4H, Ar), 7.20 (t, 4H, Ar), 5.91 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 184.5 (C=O), 169.3 (q, ^2J = 28, C-5), 138.1 (C-3), 129.1, 129, 114.9, 114.7 (6C, Ar), 118.1 (q, ^1J = 291, CF_3), 86.9 (C-4).

1,1′-Carbonyl-bis[3-(4-methoxyphenyl)-5-trifluoro-methyl-1*H*-pyrazole] (3d). This compound was obtained as a yellow solid, yield 81%, Mp. 242–244°C. ^{1}H NMR (DMSO-d_6) δ =

7.76 (d, 4H, Ar), 6.93 (d, 4H, Ar), 5.90 (s, 2H, H-4), 3.78 (s, 3H, OMe). ^{13}C NMR (DMSO-d_6) δ = 173.4 (C=O), 168.5 (q, ^2J = 28, C-5), 160.9 (C-3), 134.1, 128.5, 128.3, 113.2 (4C, Ar), 119.3 (q, ^1J = 291, CF_3), 86.5 (C-4), 55.1 (OMe).

1,1′-Carbonyl-bis[3-(4-nitrophenyl)-5-trifluoromethyl-1*H*-pyrazole] (3e). This compound was obtained as a yellow solid, yield 62%, Mp. 258–260°C. ^{1}H NMR (DMSO-d_6) δ = 8.23 (d, 4H, Ar), 7.99 (d, 4H, Ar), 5.94 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 183.1 (C=O), 170.2 (q, ^2J = 28, C-5), 148.1 (C-3), 147.3, 127.8, 123.5, 123.3 (4C, Ar), 118.3 (q, ^1J = 292, CF_3), 87.7 (C-4).

1,1′-Carbonyl-bis[3-(4,4′-biphenyl)-5-trifluoromethyl-1*H*-pyrazole] (3f). This compound was obtained as a yellow solid, yield 83%, Mp. 170–172°C. ^{1}H NMR (DMSO-d_6) δ = 8.02 (s, 4H, Ar), 7.71–7.76 (m, 8H, Ar), 7.45 (d, 6H, Ar), 6.41 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 187.3 (C=O), 170.5 (q, ^2J = 31, C-5), 143.2 (C-3), 138.9, 137.7, 137.4, 128.8, 127.9, 127.7, 126.6, 126.5 (8C, Ar), 119.2 (q, ^1J = 287, CF_3), 89.2 (C-4).

1,1′-Carbonyl-bis[3-(1-naphthyl)-5-trifluoromethyl-1*H*-pyrazole] (3g). This compound was obtained as a yellow solid, yield 74%, Mp. 186–188°C. ^{1}H NMR (DMSO-d_6) δ = 7.98–8.07 (m, 4H, Ar), 7.70–7.75 (m, 2H, Ar), 7.43–7.60 (m, 8H, Ar), 6.37 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 177.5 (C=O), 176.5 (q, ^2J = 33, C-5), 132.8 (C-3), 132.4, 129.8, 129.6, 128.2, 127.5, 126.8, 126.1, 126, 125.1, 123.7 (10C, Ar), 115.7 (q, ^1J = 293, CF_3), 94.4 (C-4).

1,1′-Carbonyl-bis[3-(thien-2-yl)-5-trifluoromethyl-1*H*-pyrazole] (3h). This compound was obtained as a yellow solid, yield 86%, Mp. 237–239°C. ^{1}H NMR (DMSO-d_6) δ = 7.63 (d, 2H, Thienyl), 7.56 (d, 2H, Thienyl), 7.08 (d, 2H, Thienyl), 5.89 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 178.9 (C=O), 168.9 (q, ^2J = 28, C-5), 149 (C-3), 129.7, 127.8, 126.9, 126.7 (4C, Thienyl), 118.7 (q, ^1J = 291, CF_3), 86.7 (C-4).

1,1′-Carbonyl-bis[3-(fur-2-yl)-5-trifluoromethyl-1*H*-pyrazole] (3i). This compound was obtained as a yellow solid, yield 67%, Mp. 259–261°C. ^{1}H NMR (DMSO-d_6) δ = 7.69 (s, 2H, Furyl), 6.90 (d, 2H, Furyl), 6.53–6.54 (m, 2H, Furyl), 5.85 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 175.8 (C=O), 169.4 (q, ^2J = 28, C-5), 155.3 (C-3), 144, 143.8, 111.7, 111.6 (4C, Furyl), 118.9 (q, ^1J = 291, CF_3), 86.8 (C-4).

1,1′-Carbonyl-bis(3-phenyl-5-trichloromethyl-1*H*-pyrazole) (9a). This compound was obtained as a white solid, yield 80%, Mp. 150–152°C. ^{1}H NMR (DMSO-d_6) δ = 7.43–7.53 (m, 2H, Ar), 7.42–7.48 (m, 8H, Ar), 6.21 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 185.6 (C=O), 175.2 (C-3), 141.8 (C-5), 130.1, 128.6, 128.1, 126.4 (4C, Ar), 100.4 (CCl_3), 83.4 (C-4).

1,1′-Carbonyl-bis(3-tolyl-5-trichloromethyl-1*H*-pyrazole) (9b). This compound was obtained as a white solid, yield 62%, Mp. 204–206°C. ^{1}H NMR (DMSO-d_6) δ = 7.68 (d, 4H, Ar), 7.21 (d, 4H, Ar), 6.36 (s, 2H, H-4), 2.33 (s, 6H, Me). ^{13}C NMR (DMSO-d_6) δ = 185.8 (C=O), 174.6 (C-3), 139.6 (C-5), 129.1, 128.6, 128.2, 126.5 (4C, Ar), 100.8 (CCl_3), 82.9 (C-4), 20.9 (Me).

1,1′-Carbonyl-bis[3-(4-chlorophenyl)-5-trichoromethyl-1*H*-pyrazole] (9c). This compound was obtained as a white solid, yield 76%, Mp. 168–169°C. ^{1}H NMR (DMSO-d_6) δ = 7.77 (d, 4H, Ar), 7,44 (d, 4H, Ar), 6.98 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 184.1 (C=O), 177.9 (C-3), 138.4 (C-5), 130.7, 130.4, 129.1, 129.0 (6C, Ar), 94.6 (CCl_3), 89.5 (C-4).

1,1′-Carbonyl-bis[3-(4-bromophenyl)-5-trichoromethyl-1H-pyrazole] (9d). This compound was obtained as a white solid, yield 64%, Mp. 142–144°C. ^{1}H NMR (DMSO-d_6) δ = 7.72 (d, 4H, Ar), 7.60 (d, 4H, Ar), 6.3 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 184.1 (C=O), 175.3 (C-3), 140.9 (C-5), 131.7, 131.0, 130.0, 128.5 (6C, Ar), 100.3 (CCl_3), 83.2 (C-4).

1,1′-Carbonyl-bis[3-(4-nitrophenyl)-5-trichoromethyl-1*H*-pyrazole] (9e). This compound was obtained as a white solid, yield 73%, Mp. 191–193°C. ^{1}H NMR (DMSO-d_6) δ = 8.30 (d, 4H, Ar), 7.71 (d, 4H, Ar), 6.32 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 178.7 (C=O), 174.9 (C-3), 148.2 (C-5), 140.5, 129.8, 123.8, 123.2 (4C, Ar), 97.0 (CCl_3), 91.8 (C-4).

1,1′-Carbonyl-bis[3-(thien-2-yl)-5-trichoromethyl-1*H*-pyrazole] (9f). This compound was obtained as a white solid, yield 68%, Mp. 183–185°C. ^{1}H NMR (DMSO-d_6) δ = 7.61 (d, 2H, Thienyl), 7.50 (d, 2H, Thienyl), 7.08 (d, 2H, Thienyl) 6.29 (s, 2H, H-4). ^{13}C NMR (DMSO-d_6) δ = 179 (C=O), 174.7 (C-3), 149.6 (C-5), 129.4, 128.7, 127.8, 126.3 (4C, Thienyl), 100.4 (CCl_3), 82.9 (C-4).

General procedure for the synthesis of ethyl 5-(trifluoromethyl)-3-phenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole-1-carboxylate (5). A solution of 5-trifluoromethyl-3-(phenyl)-5-hydroxy-4,5-dihydro-1*H*-pyrazolylcarbohydrazide (**4**) (1 mmol) and 2,4-pentanedione (1 mmol), in ethanol as solvent (4 mL) was stirred under reflux for 20 h. After the reaction time, the solvent was removed under reduced pressure. The solid residue was recrystallized from ethanol and isolated in high purity.

Ethyl 5-(trifluoromethyl)-3-phenyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole-1-carboxylate (5). This compound was obtained as a white solid, yield 63%, Mp. 127–129°C [30]. ^{1}H NMR (DMSO-d_6) δ = 8.08 (s, 1H, OH), 7.76–7.74 (m, 2H, Ar), 7.47 (s, 3H, Ar), 4.23 (q, 2H, CH_2, J = 7), 3.86 (d, 1H, H-4a, J = 19), 3.55 (d, 1H, H-4b, J = 19), 1.26 (t, 3H, CH_3, J = 7). ^{13}C NMR (DMSO-d_6) δ = 151.08 (C=O), 150.79 (C-3), 130.17, 130.09, 128.46, 126.2 (Ar), 123.4 (q, CF_3, J = 285), 91,2 (q, J = 41), C-5), 61.4 (C-4), 44.4 (CH_2), 13.9 (CH_3). GC-MS (EI, 70 eV): m/z (%) = 302 (M^+, 19), 212 (46), 189 (42), 161 (100), 77 (72).

General procedure for the synthesis of 3-(4-methylphenyl)-5-(trifluoromethyl)-1H-1-phenylpyrazole (6). A stirred solution of ketone (**3b**) (2 mmol) with phenylhydrazine (2 mmol) in 15 mL of dry ethanol was stirred at 80°C during 4 h. After the reaction time, the solvent was removed under reduced pressure, and the product **6** was dried under reduced pressure, and isolated in high purity.

3-(4-Methylphenyl)-5-(trifluoromethyl)-1H-1-phenylpyrazole (6). This compound was obtained as an oil, yield 77%. ^{1}H NMR ($CDCl_3$) δ = 7.34 (s, 5H, Ar), 7.11 (s, 4H, Ar), 6.72 (s, 1H, H-4), 2.34 (s, 3H, CH_3). GC-MS (EI, 70 eV): m/z (%) = 302 (M^+, 100), 281 (19), 233 (5), 77 (10).

General procedure for the synthesis of 5-hydroxy-3-(4-methylphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (7). To a stirred solution of ketone (**3b**) (2 mmol) in pyridine (2 mmol), was added a solution of hydroxylamine hydrochloride (2 mmol) in H_2O (1 mL). The mixture was stirred at 45°C for 24 h. After 24 h, water (25 mL) was added and extracted with diethyl ether (3 × 15 mL). The organic layer was dried with Na_2CO_3, filtered and evaporated under reduced pressure. The solid was recrystallized from diethyl ether and obtained in high purity.

5-Hydroxy-3-(4-methylphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazole (7). This compound was obtained as a yellow solid, yield 89%, Mp. 62–63°C. ^{1}H NMR ($CDCl_3$) δ = 7.53 (d, 2H, Ar, J = 8), 7.23 (d, 2H, Ar, J = 8), 3.66 (d, 1H, H-4a, J = 18), 3.47 (d, 1H, H-4b, J = 18), 2.39 (s, 3H, CH_3). GC-MS (EI, 70 eV): m/z (%) = 245 (M^+, 100), 176 (30), 133 (21), 91 (53).

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